Please add new claim 25 to read as follows:

16 ~~26~~. (new) The method of claim 15 ~~25~~, wherein said phosphatidylcholine is dilauroylphosphatidylcholine.

Please cancel claims 2-4.

REMARKS

Drawing Corrections

In compliance with 37 C.F.R. 1. 85, Applicants submit new drawings for Figs. 4-11, 13A and 13C correcting the informalities noted by the Draftsperson.

Status of the Claims

Claims 1-6, 8, 14-15, and 17-24 are pending. Claims 1-3, 5, 8, 14-15, and 17-24 are rejected herein. Claim 1 is amended herein and claims 2-4 are canceled herein. New claims 25-26 are added.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendments. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**". No new matter has been added. Reconsideration of the pending claims is respectfully requested.

Claim objections and amendments

Claim 4 is objected to as being dependent upon a rejected base claim. Claim 4 is canceled herein and the limitations of claim 4 incorporated into claim 1. Therefore, claim 1 is amended to recite a carbon dioxide-air mixture containing from about 7.5% to about 10% carbon dioxide. Thus, amendment of claim 1 in this manner overcomes 35 U.S.C. 102(e) and 103(a) rejections over **Densmore** et al. alone or in combination with **Knight** et al., **Waldrep** et al. and **Kim** et al., respectively.

Additionally, claim 1 is amended to recite a liposome as a carrier of a lipophilic drug. New claims 25 and 26 are added to further limit the type of liposome recited in amended claim 1. This matter was recited in original claims 10-13 and were canceled in the

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previous Response to Office Action filed December 4, 2001 in light of prior art disclosing the small particle aerosol delivery of such liposomes with a 5% carbon dioxide or less-air mixture. As claim 1 has been amended to limit the percentage of carbon dioxide to about 7.5% to about 10%, Applicants submit that the use of these conventional liposomes is not rendered obvious by the prior art for reasons stated *infra*.

The U.S.C. §102(e) rejections

Claims 3, 6 and 19-22 are rejected under 35 U.S.C 102(b) as being anticipated by **Densmore, Jr.** *et al.* (U.S. 6,106,859). Applicants respectfully traverse this reaction.

The Examiner states that the **Densmore, Jr.** *et al.* teaches a liposomal aerosol composition, comprising a pharmaceutical compound, a cationic lipid, a neutral co-lipid and a tryptone and further discloses the use of 5% carbon dioxide in aerosolized preparations delivered in 1 minute intervals for enhancing the deep breathing of animals and thereby the drug deposition of the transfection formulations (col. 2, lines 20-26). Additionally, the

animals were subjected to either intermittent aerosol exposure of the lipid:DNA, e.g., chloramphenicol acetyl transferase, using a jet nebulizer for 1 min. of aerosol and 9 minutes of delay in nebulization (col. 2, lines 55-67). And, furthermore, the pharmaceutical compound may be plasmid DNA and the phospholipids may be phosphatidylcholine, dimyristoylphosphatidylcholine, dilaurylphosphatidylcholine, dioleoylphosphotidylethanolamine (col. 3, lines 18-37).

Applicants have canceled claims 3 and 4. Independent claim 1 is amended, by incorporating dependent claim 4, to recite a carbon dioxide-air mixture containing from about 7.5% to about 10% carbon dioxide. Additionally, the use of a jet nebulizer to aerosolize a drug or drug-carrier formulation, including the use of a particular lipid, a particular gene or other drug, are specific features of the deposition method and are thus dependent on the method as recited in the amended claim 1. Therefore, as stated by the Examiner, the upper carbon dioxide limitation is not taught by **Densmore, Jr.** *et al.* Additionally, as claims 6 and 19-22 depend from amended independent claim 1, the features recited in these claims are also not anticipated by **Densmore, Jr.** *et al.*

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Thus, **Densmore, Jr.** *et al.* does not anticipate Applicants' claimed invention. Therefore, as this reference is not valid prior art against the instant application under 35 U.S.C. §102(e) and in view of the preceding remarks, Applicants respectfully submit that the cited reference does not anticipate claims 3, 6 and 19-22 under 35 U.S.C. §102(e). Accordingly, Applicants respectfully request that the rejection of claims 3, 6 and 19-22 under 35 U.S.C. §102(e) be withdrawn.

The U.S.C. §103(a) rejections

Claims 1-2, 17-18 and 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Densmore, Jr.** *et al.* as applied to claims 3, 6 and 19-22 above and in view of **Knight** et al. (U.S. Patent No. 6,090,407). Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Densmore, Jr.** *et al.* as applied to claims 3, 6 and 19-22 above and further in view of **Waldrep** *et al.* (U.S. Patent No. 5,958,378). Claims 14-15 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Densmore, Jr.** *et al.* as applied to claims 3, 6 and 19-22 above and further in view of **Kim** *et al.* (International

Journal of Pharmaceuticals). Applicant respectfully traverses these rejections.

Densmore, Jr. *et al.* is as previously stated for all 35 U.S.C. 103(a) rejections. **Knight** *et al.* teaches small particle lipsomes containing either water-soluble or lipid soluble anti-cancer drugs and methods of treatments. The liposomes are aerosolized via nebulization with a jet nebulizer and administered to the respiratory tract of the individual. Anti-cancer drugs may include camptothecin, taxol and their derivatives. **Waldrep** *et al.* teaches high dose pharmaceutical liposome aerosol compositions. The active agents can include anti-inflammatory glucocorticoids, immunosupressive compounds, antifungal compounds, antibiotic, anti-virals and anti-cancer compounds delivered via a high dose liposome aerosol composition in a phospholipid. **Kim** *et al.* teaches pharmacodynamics of insulin in polyethylene glycol-coated liposomes. PEG-coated DPPC liposomes have a higher incorporation efficiency, narrow size distribution and stablility *in vitro* and *in vivo* and may provide a safe and sustained injectable delivery system of other peptide and protein drugs. The Examiner states that it would have been obvious to a person of ordinary skill at the time the invention was made to

modify the process of using carbon dioxide in aerosolized compositions as disclosed in **Densmore** *et al.* by using the compositions as taught by **Knight** *et al.*, **Waldrep** *et al.* and **Kim** *et al.*

Applicants have canceled claims 2-3 and amended independent claim 1 as stated *supra*. Dependent claims 17-18 and 23-24 are drawn to various lipophilic drugs and polycationic carriers, respectively. Dependent claim 8 is drawn to water- or buffer-soluble drugs. Dependent claims 14-15 and 19 are drawn to the composition of the sterically stabilized liposomes and to various protein, peptides and polynucleotide compositions, respectively. Applicants submit that using any or all of these liposomal/sterically stabilized liposomal-drug or PEI-drug compositions with the method of **Densmore, Jr.** *et al.* does not render the instant invention obvious for the reasons stated *supra*. They are specific limitations of compositions that may be employed with the method of amended claim 1. They can not render the instant invention obvious in combination with **Densmore, Jr.** et al., if **Densmore, Jr.** et al. itself does not suggest or does not motivate one of ordinary skill in the art

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to use a carbon dioxide-air mixture containing from about 7.5% to about 10% carbon dioxide.

In view of the above remarks, Applicants respectfully submit that obviousness can not be established by combining the teachings of the prior art absent some teaching, suggestion or motivation supporting the combination to do so. Absent a suggestion or teaching in **Densmore, Jr.** *et al.* of using a carbon dioxide-air mixture which, at a minimum, is 50% higher than **Densmore, Jr.** *et al.* taught, Applicants' invention, as recited in amended claim 1, is not rendered obvious by combining **Densmore, Jr.** *et al.* with any of **Knight** *et al.*, **Waldrep** *et al.* or **Kim** *et al.* Thus, the invention as a whole was not obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, Applicants respectfully request that the rejection of claims 1-2, 8, 14-15, 17-19, and 23-24 under 35 U.S.C. §103(a) be withdrawn.

This is intended to be a complete response to the Office Action mailed January 30, 2002. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution. Should any fees be due,

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please debit Deposit Account 07-1185 on which the undersigned is allowed to draw.

Respectfully submitted,

Date: Feb 22, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please amend claim 1 as follows:

1. (twice-amended) A method of increasing the deposition of a drug into the respiratory tract of an individual or animal during inhalation therapy, comprising the steps of:

mixing carbon dioxide gas with air to form a carbon dioxide-air mixture, said carbon dioxide-air mixture containing ~~up~~ about 7.5 % to about 10% by volume carbon dioxide gas;

aerosolizing said drug in said carbon dioxide-air mixture wherein prior to aerosolization said drug is a soluble drug dissolved in a buffered solution or water or, in the alternative, said drug is an insoluble or lipophilic drug carried by a liposome, a sterically stabilized liposome, a slow release polymer or a polycationic polymer; and

administering said aerosolized drug during inhalation therapy by continuously flowing said carbon-dioxide-air mixture wherein carbon dioxide in said mixture increases inhalation rate and

inhaled volume of said aerosolized drug thereby increasing deposition of said aerosolized drug into the respiratory tract.

Please add new claim 25 as follows:

25. (new) The method of claim 1, wherein said liposome is formed from a lipid comprising a phosphatidylcholine.

Please add new claim 26 as follows:

26. (new) The method of claim 25, wherein said phosphatidylcholine is dilauroylphosphatidylcholine.

Please cancel claims 2-4.